REMARKS

Claims 33-64 are all the claims pending in the application. Applicants herewith amend claim 33, support for which is found at least at paragraph 47 of the published application. Support for the Amendment to claim 35 is found at least at paragraph 82 of the published application. Support for the Amendment to claim 50, 61 and 64 is found at least at paragraphs 97, 103, and 87 of the published application. Support for the Amendment to claims 59 and 62 is found at least at paragraph 87 of the published application. Support for the Amendment to claim 63 is found at least at paragraph 88 of the published application. No new matter is added. Entry of the Amendment is therefore kindly requested.

I. Response to Restriction Requirement

Applicants thank the Examiner for acknowledging Applicants' election without traverse of Group A, claims 33-37, 40-42, 53-56 in the reply filed on May 23, 2007.

II. Claims 33, 25, 27, 40, 41, 42, 60, 61 and 64 are Proper

At page 2 of the Office Action, the Office objects to claims 33, 37, 40, 41, and 42 for abbreviations and recitation of "a first coding region" and "a region having at least one restriction site" in claim 35; recitation of "being" and "and is translated in the same reading frame to be a protease digestion site" in claim 35; and recitation of "being" and "and is translated in the same reading frame to be a protease digestion" in claim 35; and recitation of "making express the fused protein in cytoplasm" in claim 60; recitation of "a first coding region" or "a second coding region" in claim 61; and recitation of "a protease digestion site" in claim 64.

To advance prosecution, Applicants herewith amend the claims without prejudice or disclaimer. Applicants' amended claims overcome the rejections.

Withdrawal of the objections is therefore kindly requested.

III. Claims 59-64 Are Definite Under 35 U.S.C. § 112, Second Paragraph

At page 3 of the Office Action, the Office rejects claims 59-64 under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite.

To advance prosecution, Applicants herewith amend the claims without prejudice or disclaimer. Applicants' amended claims overcome the rejections.

Withdrawal of the objections is therefore kindly requested.

IV. Claims 33-37, 40-42, 53-56 and 59-64 Are Adequately Described Under 35 U.S.C. § 112, First Paragraph

At page 4 of the Office Action, the Office rejects claims 33-37, 40-42, 53-56, and 59-64 under 35 U.S.C. § 112, first paragraph, as allegedly lacking a written description.

In making the rejection, the Office asserts that the specification teaches "representative" species of sequences encoding a PPIase having molecular chaperone activity but that the specification does not identify characteristics or properties of other species that have molecular chaperone activity.

Applicants respectfully disagree with the Examiner. Applicants teach vectors encoding various PPIases fused to various genes. Numerous representative PPIases are explicity disclosed in the specification and include TcFKBP18 (Example 1, 8 and 9); trigger factor-type (Exampes 2 and 10); FKBP52-type (Examples 3 and 11); CyP40-type (Examples 4 and 12, FK_pAT-type (Examples 5 and 13); and SurA-type (Examples 6 and 4). Thus, various species are explicitly set forth which is a sufficient number under current law. A written description is not adequate if a compound is described *only* by its function because finding a representative compound then becomes a trial-and-error process. *University of Rochester v. G.D. Searle & Co*, 249 F. Supp. at

221 (wherein the Court held that if a description lacks any suggestion that the inventors had identified so much as one compound that would be suitable for use in practicing the claimed invention an adequate written description is not found). Teachings of *as few as two* species are adequate written description support for claims directed to a genus. *Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 126 F. Supp. 2d 69, 148-49 (D. Mass. 2001), *aff'd in part, vacated in part*, 314 F.3d 1313 (Fed. Cir. 2003) (wherein the Court held that Applicants' disclosure of erythropoietin production in two mammalian cell lines was adequate to inform one of ordinary skill that Applicants' invention encompassed erythropoietin production in any cultured mammalian cell because the claim terms are known to ordinarily skilled artisans). In the present application, Applicants do not only define the claimed vectors by their function, but show numerous specific vectors containing numerous PPIases fused to numerous genes. PPIases are known in the art to function to refold a denatured protein into an original conformation. Numerous examples of such proteins are well known in the art and are set forth in at pages 8-18 of the specification and Applicants' Examples. Thus, Applicant's claim term (e.g., PPIase) is known to one skilled in the art and described in the specification. Applicants also describe the invention using numerous sequences, functional assays and figures. The Examiner's general assertion that more is required is not consistent with the law. Without evidence of why a person skilled in the art would not recognize that the written description provides support for the claims the Examiner cannot maintain a *prima facie* case of lack of written description.

Accordingly, withdrawal of the written description rejection is therefore kindly requested.

V. Claims 33-37, 40-42, 53-56, and 59-64 Are Enabled Under 35 U.S.C. § 112, First Paragraph

At page 5 of the Office Action, the Office rejects claims 33-37, 40-42, 53-56, and 59-64 under 35 U.S.C. 112, first paragraph, as allegedly lacking enablement.

Applicants respectfully disagree. The Examiner attempts to support the lack of enablement rejection by stating that modification of an amino acid sequence is unpredictable and that all sequences are intolerant to modification; that multiple substitutions do not routinely yield functional proteins; and that regions of the PPIase are not disclosed which are necessary for generating PPIase mutants. The claims clearly recite PPIases, not mutated PPIases. The Examiner cites to case law stating that the scope of the claims must bear a reasonable correlation with scope of enablement. *In Re Fisher*, 421 F3d 1364. However, the holding in *Fisher* pertains to utility, which is not the basis of a rejection in the outstanding Office Action. Further, the subject matter in *In re Fisher* was directed to ESTs with unknown functions, not well defined, fully characterized, functionally described PPIases common to those of ordinary skill in the art. The Court held that Fisher's ESTs provided only guesses as to their use, a standard too far below that required for patentability. Applicants' disclosure, however, is not a mere disclosure of a polynucleotide sequence to a putative polypeptide with no known function. The application teaches numerous vectors containing numerous PPIases which are know to function with certainty in the art. The facts are therefore dissimilar to those in *In re Fisher.* The rejection cannot be maintained based on the application of a Court holding that is non-binding and inapplicable.

The Examiner also cites to *In re* Wards to support the rejection. The present facts resemble those under review in *In re Wands*, 858 F.2d 731, (Fed. Cir. 1988), wherein the Court reversed the Examiner's rejection for lack of enablement holding that undue experimentation

would not be required to practice the invention because it is know that in producing antibodies it is routine to first make monoclonal hybridomas to determine which hybridomas secrete antibodies with the desired characteristics. The Court found that the specification provided representative working examples as well as the methods needed to practice the invention. Like in the present case, Wands conducted successful experiments and produced evidence that at least one representative embodiment fell within the scope of the claims. Applicants provide many.

In addition, the Office is respectfully reminded that to meet the goal of reaching a clearly defined issue for an early termination of proceedings, i.e., issuance of an Office Action, the Examiner is charged with conducting a careful and thorough search and fully applying the references in preparing the first Office Action on the merits in order for a speedy and just determination of the issues involved in the examination of the application. See MPEP §§ 706.07 and 904.03. Because the enablement rejection is grounded in limitations not recited by the claims (e.g., mutant PPIases), it appears the specification and claims were not duly considered prior to issuance of the outstanding Office Action. Applicants therefore kindly request that the rejection be withdrawn as premature and lacking grounds.

Withdrawal of the lack of enablement rejection is therefore kindly requested.

VI. Claims 33-37, 40-42, 53-56 and 59-64 are Patentable Under 35 U.S.C. § 103(a)

At page 9 of the Office Action, the Office rejects claims 33-37, 40-42, 53-56, and 59-64 under 35 U.S.C. § 103(a) as being unpatentable over Fersht et al. (WO 00/75346) in view of Furutani et al. The Examiner alleges that Fersht et al. teaches expression vectors for producing a fusion protein comprising a chaperone polypeptide fused in frame to a protein of interest but that the cited reference does not teach a PPIase having molecular chaperone activity. The Examiner

further states that Furutani et al. disclose recombinant PPIase from *Methanococcus thermolithotrophicus*, a protein that has molecular chaperone activity.

Applicants respectfully disagree that the cited references render the claims obvious. Ferscht et al. does not teach each and every element of Applicants invention because Ferscht et al. disclose a vecotor having a first coding region encoding a fragment of a chaperon in a polypeptide to aid in the gene expression. Example 1, Ferst et al. The 191-345 GroEl fragment does not have molecular chaperone activity. Ferscht et al. do not suggest nor motivate one skilled in the art to use a chaperone fusion protein in order to obtain soluble proteins.

Attached please find the Declaration Under 37 C.F.R. § 1.132 of Dr. Ideno. Dr. Ideno compared the expression of Applicants' TcFk fusion 2 system to the expression in the GroEl (191-345) fusion system of Fersht et al. Pages 3-4, Declaration. The level of total soluble fusion protein present in the cellular fraction using Applicants' invention was about 14%. However, no expression was detectable using the Fersht et al. system. Figure 2, page 7. The results of the direct comparative analysis are shown at page 5, Table 1.

The evidence presented in Dr. Ideno's Declaration establishes that, contrary to the Examiner's assertion that Fersth et al. teach vectors for producing fusion proteins comprising a fusion-chaperone polypeptide, the Fersht et al. system does not teach the elements of Applicant's invention because the chaperone fragment of Fersht et al. does not have molecular chaperone activity.

Furtani et al. fails to remedy the deficiencies of Fersht et al. because Furtaini et al. does not disclose Applicants' vectors. Thus, it is impossible to establish a prima facie case of obviousness based on the references as cited by the Examiner since essential elements of Applicants' invention are not disclosed. Furthermore, the Examiner fails to state a reason that

would have prompted a person of ordinary skill in the art relevant field to combine the elements in the way the claimed new invention does because the elements are not disclosed. *KSR International Co. v. Teleflex, Inc.*, 550 U.S. ____ (2007).

Accordingly, withdrawal of the obviousness rejection is requested.

In view of the above, reconsideration and allowance of this application are now believed to be in order, and such actions are hereby solicited. If any points remain in issue which the Examiner feels may be best resolved through a personal or telephone interview, the Examiner is kindly requested to contact the undersigned at the telephone number listed below.

The USPTO is directed and authorized to charge all required fees, except for the Issue Fee and the Publication Fee, to Deposit Account No. 19-4880. Please also credit any overpayments to said Deposit Account.

Respectfully submitted,

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